ATTACHMENT B

REMARKS

By this Amendment, in accordance with the suggestions of the Examiner, Applicants have now amended Claim 1 to refer to a monoclonal antibody having the specific properties which further distinguish it from the prior art and have made other minor changes to the dependent claims to conform to the amendments to Claim 1. The amendments to Claim 1 are well supported in the specification and in fact were made in accordance with the suggestions of the Examiner in the Official Action. The dependent claims have been amended to be consistent with the language of amended Claim 1, and Claims 3 and 23 have been canceled without prejudice since these features are now incorporated into Claim 1. In light of the amendments made herein and the arguments set forth below, Applicants submit that all outstanding rejections have been overcome and that the present application has been placed in condition for allowance.

In the Official Action, the Examiner rejected Claims 31 and 32 on the basis of 35 U.S.C. §112 that they constituted new matter. This rejection is respectfully traversed in that the specification clearly discloses that the present antibodies are capable of inhibiting T lymphocyte activity in a host cell, and this is disclosed throughout the original specification, e.g., at paragraph 0038 ("As the present inventors have determined, the propeptide, Pep_{263} constitutes a superantigen-like moiety which is released from Int1p and **which plays a major role in activating T lymphocytes in host cells**. Accordingly, **an antibody or other agent capable of binding to this propeptide can be utilized in a method of disrupting the activation of T lymphocytes caused by microorganisms such as *C. albicans*** and *S. cerevisiae*,

and thus can be utilized in methods of preventing, treating, or reducing the virulence of infections from such microorganisms which express Int1p.") (emphasis added). In addition, the fact that the present invention is directed to treatment of infections from *Candida albicans* is disclosed throughout the application, and the fact that Candida infections operate on epithelial and endothelial cells is also clearly disclosed in the specification, see, e.g., paragraph 0004 ("It is well recognized **that *C. albicans* adheres to epithelial and endothelial cells in the human host**, often times by recognizing proteins of the extracellular matrix called ligands.") (emphasis added).

Accordingly, it is clear that there is support in the specification for Claims 31 and 32 and that the Examiner's objection on that basis is respectfully traversed.

In the Official Action, the Examiner rejected the claims on the basis of specific objections to Claim 1 and Claim 3. This rejection is respectfully traversed in the present amendments in that the Examiner's suggestion with regard to the language of the propeptide has been adopted, and the subject matter of Claim 3 relating to the cleavage of the propeptide (which has now been incorporated into Claim 1) has been modified so that it is clear that the propeptide is cleaved from the Int1p protein, and this process leads to the activation of T lymphocytes. As indicated below, the present monoclonal antibodies in accordance with the invention are capable of preventing the cleavage of the propeptide from the Int1p protein in an unexpected manner and thus allows the invention to be effective in inhibiting T lymphocyte activation in a manner not previously achieved by prior antibodies to *Candida albicans*. Accordingly, the Examiner's rejections under Section 112 are respectfully traversed and should be withdrawn.

In the Official Action, the Examiner made a series of rejections based on the lead inventor's prior patents, namely U.S. Pat. No. 5,886,151 and 6,774,219, and as was pointed out in a Declaration of inventor Hostetter in a prior response, neither of these patent references (which are from the same patent family wherein 6,774,219 is merely a divisional of a divisional application of 5,886,151), discloses or suggests a monoclonal antibody in accordance with the present invention which is capable of preventing the Int1p propeptide from being cleaved and which is capable of thereby inhibiting the activation of T lymphocytes. These rejections include an obviousness-type double patenting rejection on the basis of Hostetter U.S. Pat. No. 6,774,219, a rejection under 35 U.S.C. §102(b) on the basis of Hostetter U.S. Pat. No. 5,886,151, a rejection under 35 U.S.C. §102(b) on the basis of Hostetter U.S. Pat. No. 6,774,219, and rejections to Claims 9 and 11 as obvious in light of Hostetter U.S. Pat. No. 5,886,151. These rejections, insofar as applied to the claims as amended, are respectfully traversed.

In the first place, the Examiner indicated in the Official Action that her position was premised on the fact that the prior claims were not limited to monoclonals of the type that have been shown to successfully prevent cleavage of the propeptide and to successfully inhibit the activation of T lymphocytes. See, e.g., pages 4-5 of the Official Action. This position is respectfully traversed in that Applicants have now directed their claims to a monoclonal antibody having the specific properties as disclosed in the original specification, and which were discussed in the Declaration previously provided by Dr. Hostetter.

Moreover, Applicants previously prevented evidence in the form of a Declaration that the prior Hostetter patents did not disclose or suggest any monoclonal antibody to

the propeptide region, much less one that was capable of preventing cleavage of the propeptide and inhibiting T lymphocyte activity. Indeed, the prior antibodies resulting from the inventor's prior work as reflected in the cited Hostetter patents did **not** have the ability to inhibit T lymphocyte activation, as was shown in the prior Declaration. In this regard, the Examiner's position that such antibodies would inherently have that activity is refuted since the prior antibodies were tested and did **not** show such activity. In light of the fact that Applicants' evidence has shown that the none of the polyclonal antibodies referred to in the prior citations had the activity as required in the claims, and that no monoclonals to any specific region were disclosed or suggested, much less ones with the specific properties of the monoclonal antibody as presently claimed, the Examiner's position that the prior Hostetter patents inherently disclosed the present invention is respectfully traversed.

In addition, the Examiner makes constant reference to an alleged peptide disclosed in the prior Hostetter cases which purportedly has an extremely minor portion of its sequence in common with the propeptide region of the Int1p protein as claimed in the present application. However, this clearly does not anticipate or make obvious Applicants' invention because there is certainly no disclosure or suggestion in the prior patents of a specific epitope that could be used to generate any antibodies, much less one that would be used to generate the specific monoclonal antibody having the properties of the present invention. Indeed, the fact that prior antibodies generated as disclosed in the cited patents did **not** exhibit the activity of the monoclonal antibodies of the present claims, namely the ability to inhibit the activity of T lymphocytes.

Even further, while it is true that polyclonal antibodies may recognize multiple epitopes of a protein, it is the opposite with monoclonal antibodies which generally are made so as to recognize a specific epitope. Thus, there is clearly no teaching or suggestion in the prior Hostetter patents of a monoclonal antibody to the propeptide region, much less one which exhibits the properties of the monoclonal antibodies of the present invention. The fact that polyclonal antibodies as recited in the prior Hostetter patents did not exhibit inhibition of T lymphocyte activity would thus teach away from the presently claimed invention wherein monoclonal antibodies to the propeptide have the ability to prevent propeptide cleavage and thus reduce the activation of T lymphocytes.

Finally, the Examiner's suggestion that antibodies which recognize a particular region on an amino acid sequence would inherently recognize another peptide with that same region is not correct, and this is particularly true with regard to monoclonal antibodies which are generated against an epitope which might be greatly removed from a particular sequence and would not recognize such a sequence. For example, as indicated in the attached Appendix with regard to other microorganism binding proteins, tests were conducted with regard to monoclonal antibodies to various regions of the CNA binding protein, and antibodies to the CBD region 61-343 did **not recognize any other region**, including the **lesser included regions** such as the present region 151-318 or the region 151-297 (which was also not recognized by an mAb to the region 30-531). Thus, even though there may be overlap between the binding regions recognized by two different monoclonal antibodies, because monoclonals are to specific epitopes, it is not the case that such antibodies will recognize the other region.

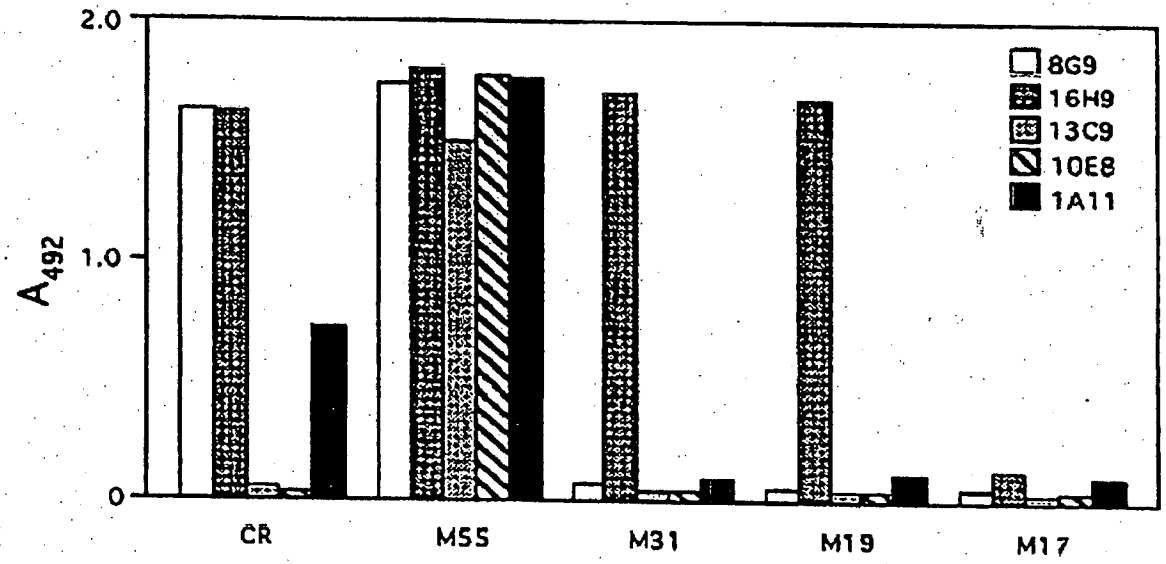
In the present case, there is no disclosure or suggestion in the prior Hostetter patents to prepare a monoclonal antibody directed to the specific propeptide region of Int1p, no disclosure or suggestion in any way that any antibodies generated therein would act to inhibit T lymphocyte activity, and indeed such antibodies **did not** actually exhibit inhibition of T lymphocytes. Accordingly, the claims of the present application which are directed to monoclonal antibodies which bind to the propeptide region and prevent cleavage of the propeptide from Int1p and thus inhibit activation of T lymphocytes are clearly not disclosed or anticipated in those prior Hostetter references, and in fact obtain substantial unexpected benefits over the antibodies of the prior art. Accordingly, the prior references do not anticipate or make obvious Applicants' claimed invention, and the Examiner's rejections on the basis of the prior Hostetter patents, insofar as applied to the present claims, are respectfully traversed and should be withdrawn.

In light of the amendments and arguments as set forth above, as well as the attachments provided herewith, Applicants submit that the present application has been placed in condition for immediate allowance, and such action is earnestly solicited.

END OF REMARKS

APPENDIX

ELISA analysis of immobilized recombinant constructs of collagen binding MSCRAMM



Five antibodies were analyzed by ELISA for their ability to bind portions of the collagen binding MSCRAMM. Antibody 16H9 recognized the fragment M55 (CBD 30-529), M31 (CBD 61-343) and M19 (CBD 151-318), but not M17 (151-297). The other four antibodies only recognized the largest portion of the collagen binding MSCRAMM. These data clearly demonstrate that antibody recognition of an epitope in a larger protein does not ensure that the antibody will also recognize a smaller portion of the same protein. CR= native collagen receptor from *S. aureus*.